Proteins with large influence on network dynamics evolve slowly

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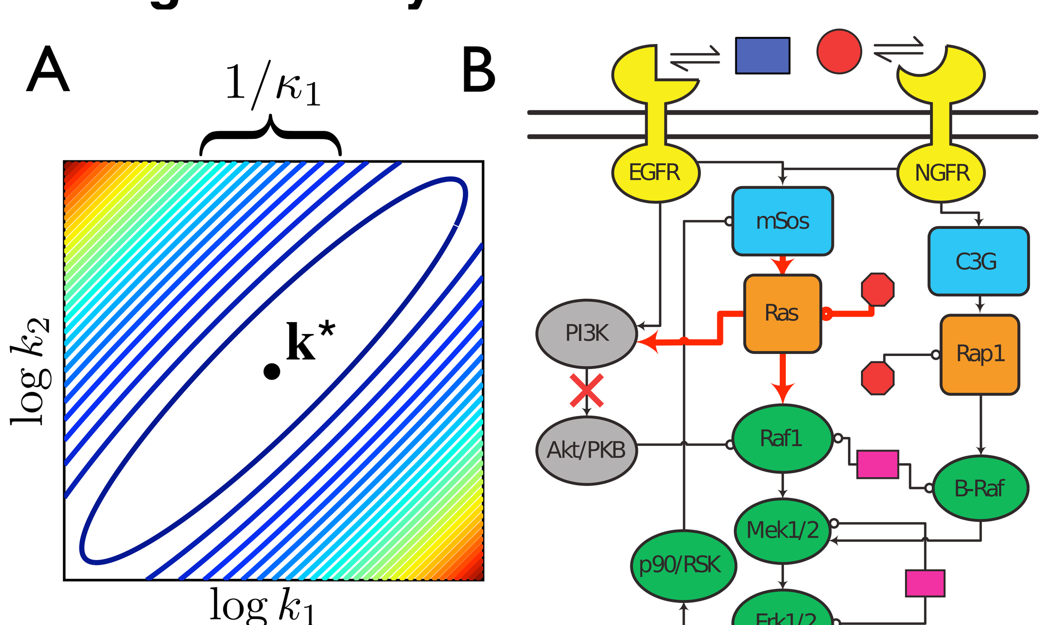
Summary

Studies of protein evolution typically take a coarse view of protein function. Here I take a much finer view, using detailed mechanistic models to measure the influence of each constituent protein on its network's dynamics.

I show that a protein's dynamical influence and its evolutionary rate are negatively correlated, implying purifying selection on network dynamics. Correlation coefficients are typically of order -0.3, among the strongest known correlates of evolutionary rate. Moreover, this correlation is independent of interaction degree, expression level, and knock-out essentiality.

Dynamical influence

Figure 1 - Dynamical influence



The inclusive measure of dynamics, χ^2, sums over all dynamical species in the network [Gutenkunst (2007)].

$$\chi^2(\mathbf{k}) \propto \sum_y \int \left(\frac{y(t,\mathbf{k}) - y(t,\mathbf{k}^*)}{\sigma_y}\right)^2 \mathrm{d}t$$

The dynamical influence κ_i of parameter i is (see **Figure 1A**)

$$\kappa_i = \sqrt{\frac{\partial^2 \chi^2}{\partial^2 \log k_i}}.$$

The dynamical influence $\mathcal{I}$ of a protein is the mean influence of parameters governing reactions the protein participates in.

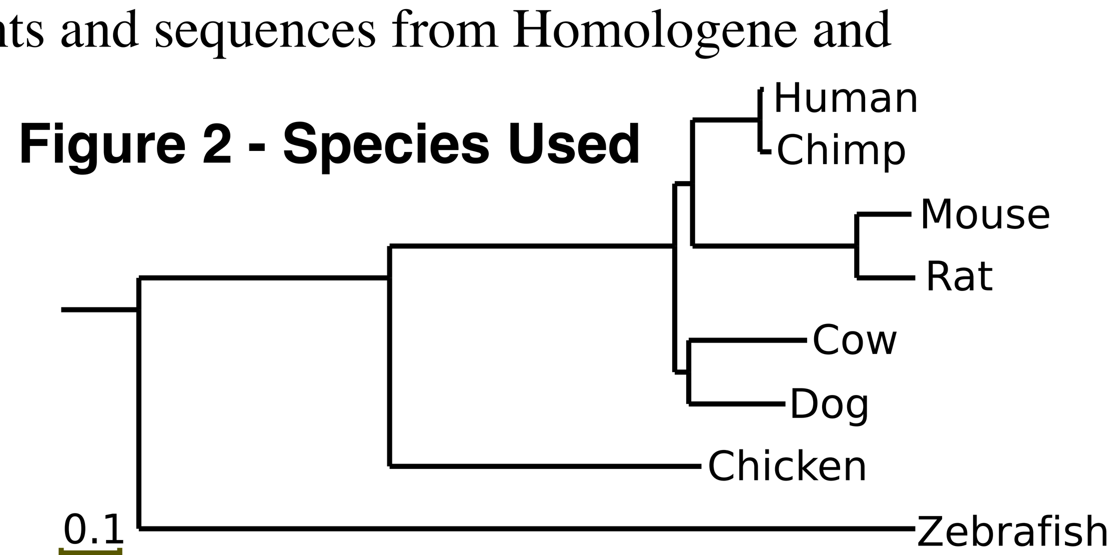
$$\mathcal{I} = \langle \kappa_i \rangle_{\text{geom}}$$

For example, in the network shown in **Figure 1B** the influence of Ras incorporates all the highlighted reactions.

Evolutionary rate

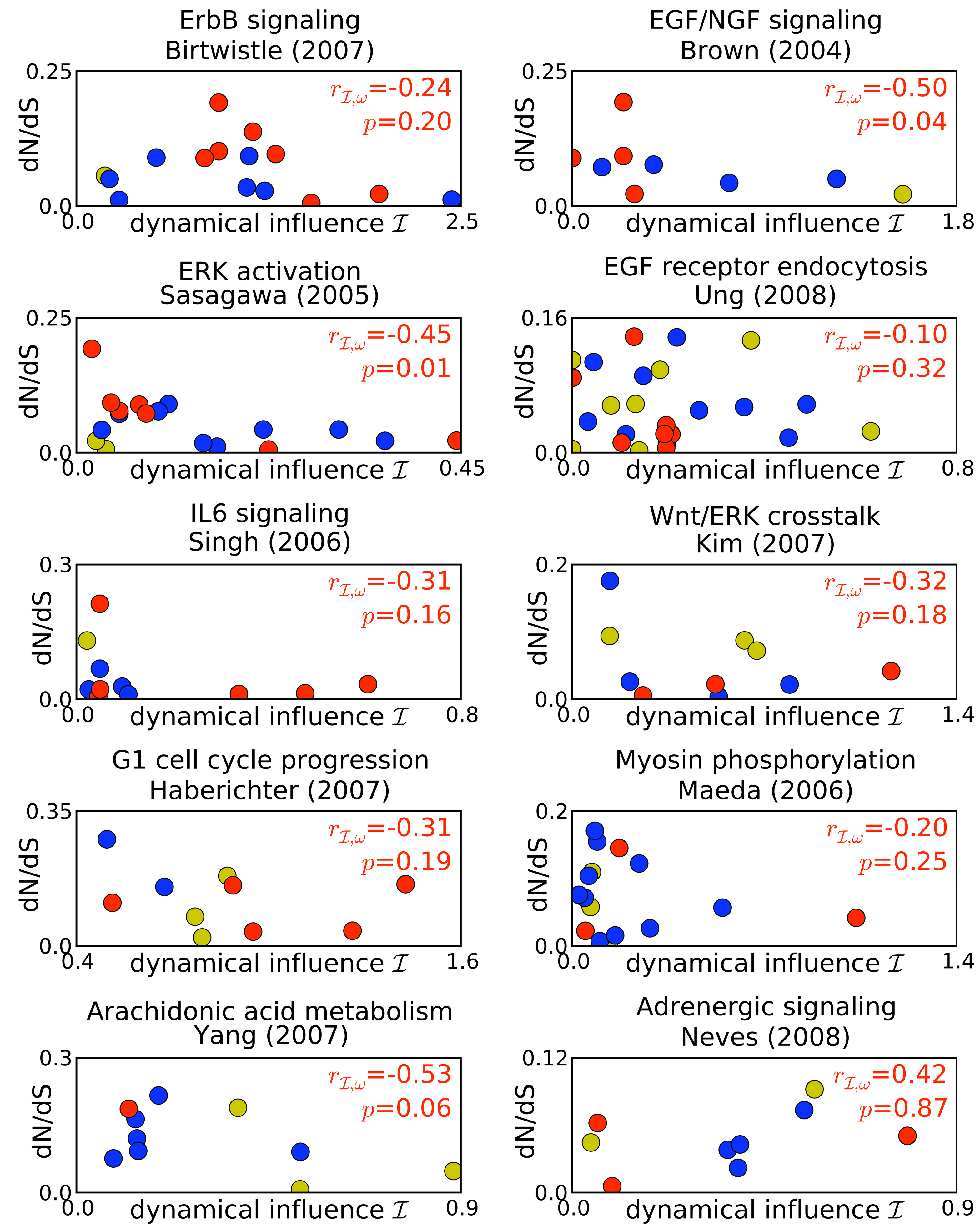
Maximum-likelihood dN/dS values were inferred with PAML, using alignments and sequences from Homologene and GenBank.

Figure 2 - Species Used



Data

Figure 3 - Correlation in real networks



Knock-out essentiality in mouse:
-essential -nonessential -no data

I tested all models in the BioModels database possessing 8 or more species annotated with Uniprot identifiers. Results are shown in **Figure 3**. As seen, for 9 out of 10 models there is a negative correlation between evolutionary rate and dynamical influence. Individual p-values are not dramatic, because model development is inherently low-throughput. However, it is compelling that so many systems show the expected correlation.

Note, the first 5 models all include an experimentally manipulated protein ligand, which I have removed from these analyses. I also omit the influence of multi-protein complexes, as it is not annotated which protein in a complex is active for each reaction. *p*-values are from one-sided permutation tests.

Other potential correlates

It is known that protein evolutionary rates correlate with number of interaction partners (interaction degree), level of expression, and knock-out gene essentiality. I use the number of reactions *R* a protein is involved in (including complexes) as a proxy for interaction degree. I use the total amount *X* of a protein in the model as a proxy for expression. Essentiality in mouse *K* is measured using knock-out data from the Mouse Genome Database. **Table 1** compares the correlations with and without controlling for these variables. It can be seen that these variables typically have little influence on the strength of correlation.

Table 1 - Correlations and partial correlations

Model	$r_{\mathcal{I}\omega}$ (*p*-val)	$r_{\mathcal{I}\omega,R}$	$r_{\mathcal{I}\omega,X}$	$r_{\mathcal{I}\omega,K}$
Birtwistle (2007)	-0.24 (0.20)	0.21	0.14	-0.31
Brown (2004)	-0.51 (0.04)	-0.38	-0.64	-0.56
Sasagawa (2005)	-0.45 (0.01)	-0.45	-0.46	0.21
Ung (2008)	-0.10 (0.32)	-0.15	-0.07	-0.47
Singh (2006)	-0.31 (0.16)	-0.35	-0.48	-0.36
Kim (2007)	-0.32 (0.17)	-0.34	-0.36	-0.25
Haberichter (2007)	-0.31 (0.19)	-0.50	-0.69	-0.10
Maeda (2006)	-0.20 (0.26)	-0.18	-0.22	-0.22
Yang (2007)	-0.53 (0.06)	-0.54	-0.65	-0.15
Neves (2008)	0.42 (0.87)	0.60	0.55	0.35

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